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Letter to the Editor

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Effect of antihypertensive agents ACEI/ARB and CCB on hypertensive intracerebral hemorrhage and inflammatory cytokines, serum ferritin, and serum P

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Abstract

The aim of this study was to investigate the effect of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and calcium channel blocker (CCB) antihypertensive drugs on the treatment of hypertensive intracerebral hemorrhage (ICH) and on the expression level of inflammatory factors, serum ferritin (SF), and serum substance P (SP). A total of 160 patients with hypertensive ICH were divided into three groups according to the type of antihypertensive drugs taken before cerebral hemorrhage: group A (40 cases, taking ACEI/ARB antihypertensive drugs before cerebral hemorrhage), group B (40 cases, CCB antihypertensive drugs were regularly taken before the onset of cerebral hemorrhage), and C group (80 cases, nor any antihypertensive drugs were regularly taken before the onset of cerebral hemorrhage). Patients in group C were further divided into two groups: group D (40 cases, ARB antihypertensive drugs were regularly taken after cerebral hemorrhage) and group E (40 cases, CCB antihypertensive drugs were regularly taken after cerebral hemorrhage). On the third day, after the onset of disease, the level of serum interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, SF, and SP in all the patients was detected. At the same time, the brain computed tomography (CT) was used to evaluate the cerebral edema. On the first day and the thirty day after the onset of disease, the patient's neurological deficit status was assessed according to the National Institutes of Health Stroke Scale (NIHSS) score. On the third day after onset, the levels of IL-1β, IL-6, TNF-α, SF, and the volume of cerebral edema in group A and group B were significantly lower than those in group C ($P < 0.05$). The level of serum SP in group A and group B was significantly higher than that in group C ($P < 0.05$). However, there was no significant difference between group A and group B ($P > 0.05$). On the third day after onset, the mortality of each group is of no significant difference ($P > 0.05$). However, NIHSS scores in group A and group B were significantly lower than those in group C ($P < 0.05$). There was no statistical difference in NIHSS scores between group A and group B ($P > 0.05$). In conclusion, in the early stage of hypertensive ICH, early normative use of ACEI/ARB or CCB antihypertensive drugs can improve the prognosis of patients, whose mechanism may be related to the improvement of level of serum inflammatory factors and SP and SF.

Keywords

antihypertensive drugs, cerebral hemorrhage, hypertension, inflammatory cytokines, serum ferritin, serum substance P

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Introduction

Intracerebral hemorrhage (ICH) is a clinical critically disease, referring to the bleeding caused by non-traumatic intraparenchymal blood vessels rupture, whose common causes include hypertension

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with arteriosclerosis, aneurysms, and cerebrovascular malformations.[1] Long-term hypertension leads to intracranial atherosclerosis, causing weakness of vessel wall, followed by small aneurysms, blood pressure surge, small aneurysm rupture, and the formation of primary cerebral hemorrhage injury, subsequently the formation of hematoma in hemorrhage area, which in turn expands to the surrounding brain tissue leading to edema, resulting in secondary injury. Cerebral edema generally reached its peak at 48 h of the onset and sustained 3 days to 3 weeks.[2] It can increase intracranial pressure and even lead to the formation of herniation, which is an important influential factor on the prognosis of hypertensive ICH.[2] Actually, inflammatory factors play an important role in the formation of cerebral edema.[3] It has also been found that both angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) antihypertensive drugs and calcium channel blocker (CCB) antihypertensive drugs enable to regulate the level of inflammatory cytokines such as serum interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α).[4] Pericranial edema in patients with hypertensive ICH can be reflected by serum ferritin (SF) and substance P (SP) levels.[5] At present, there are few reports about the influence of different antihypertensive drugs on the level of serum inflammatory cytokines, SF and SP, in patients with hypertensive ICH. Thus, this study was to investigate the effect of ACEI/ARB and CCB antihypertensive drugs on the treatment of hypertensive ICH and on the expression level of inflammatory factors SF and SP.

Materials and methods

Subjects

A total of 160 hospitalized hypertensive ICH patients were selected from July 2014 to December 2016 in our department. Inclusion criteria are as follows: (1) The diagnostic criteria for hypertensive ICH should be met and the diagnosis of cerebral hemorrhage should be confirmed by cerebral computed tomography (CT) and/or magnetic resonance imaging (MRI; bleeding volume 10–30 mL). (2) The patient should have the first episode of cerebral hemorrhage and is admitted to hospital within 24 h of onset to receive treatment. (3) The awareness of patient is clear. (4) Hypertension treatment regimen is ACEI/ARB or CCB antihypertensive drug monotherapy or the patient did not receive any formal treatment. Exclusion criteria are as follows: (1) brainstem or cerebellar hemorrhage; (2) use of antihypertensive drugs other than ACEI/ARB and CCB, including a variety of diuretics and sympathetic nerve blockers; (3) combination of a variety of antihypertensive drugs; (4) the patients are with serious disturbance of consciousness; (5) the patients are with serious heart, liver, and kidney dysfunction; (6) lactating or pregnant women; and (7) drug allergy.

A total of 160 patients were divided into three groups according to the presence or absence of antihypertensive drugs before admission. Group A (40 patients, ACEI or ARB antihypertensive drugs were regularly taken before admission), group B (40 patients, CCB antihypertensive drugs were regularly taken before admission), and group C (80 cases, any antihypertensive drugs were not formally taken before admission). Patients in group C were further divided into two groups randomly and were assigned to group D (40 cases, ARB antihypertensive drugs were regularly taken after admission) and group E (40 cases, CCB antihypertensive drugs were regularly taken after admission). All patients were informed and agreed of the study.

Treatment

All patients were received the basic treatment, including reducing intracranial pressure, maintaining blood glucose and keeping electrolyte balance, preventing complications, and performing fluid support. Patients in group A and group B continued their prehospital program of antihypertensive treatment. Patients in group D received valsartan 80 mg QD, and the maximum dosage is 160 mg. Patients in group E received nifedipine 30 mg QD, and the maximum dosage is 60 mg.

Assessment markers

The level of serum IL-1β, IL-6, TNF-α, SF, and SP of all patients on the third day of onset was detected using radioimmunoassay, enzyme-linked immunosorbent assay, and latex-enhanced immunostaining assay. Patients under fasting were drawn 3 mL ventrical blood in the early morning

Table 1. The baseline data comparison among the three groups (case, %).

Group	Case	Age (years)	Sex (male/female)	Diabetes	Admission systolic blood pressure (mmHg)	Admission diastolic blood pressure (mmHg)	Hypertension lasting time			Admission NIHSS scores (score)	Admission cerebral hemorrhage volume (mL)
							1–5 years	6–10 years	⩾10 years		
Group A	40	57.54 ± 9.25	20/20	4 (10.00)	153.61 ± 4.54	94.44 ± 13.27	18 (45.0)	13 (32.5)	9 (22.5)	17.56 ± 7.08	20.78 ± 7.33
Group B	40	56.86 ± 8.13	21/19	3 (7.50)	154.55 ± 4.12	95.03 ± 12.18	19 (47.5)	11 (27.5)	10 (25.0)	17.34 ± 6.95	20.86 ± 7.65
Group C	80	57.15 ± 9.04	40/40	9 (11.25)	157.82 ± 3.76	96.18 ± 12.06	40 (50.0)	26 (32.5)	14 (17.5)	18.28 ± 7.43	21.94 ± 7.72
F/χ^2		1.09	1.41	1.16	0.92	0.55	0.75			1.32	0.94
P		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05			>0.05	>0.05

NIHSS: National Institutes of Health Stroke Scale.

of the check day. All tests were completed by our hospital laboratory.

Cranial CT was performed to assess the cerebral edema

On the third day of onset, the cranial CT was reviewed to assess the condition of cerebral edema. The volume of cerebral hemorrhage and edema volume were calculated according to Tian's formula, that is, the maximum cross section of the long axis × the largest cross section of the short axis × bleeding surface (or edema level) × π/6; brain edema volume = edema volume − volume of cerebral hemorrhage.

National Institutes of Health Stroke Scale score and mortality

All patients were scored on National Institutes of Health Stroke Scale (NIHSS) on the first day and the 30th day of onset, and 30-day mortality was calculated for each group.

Statistical analysis

SPSS 21.0 software was used for data processing. The measurement data were indicated with the $\bar{x} \pm SD$ to test the normality and homogeneity of variance. One-way analysis of variance (ANOVA) was used for the comparison among three groups, and Student–Newman–Keuls (SNK)-q test was used for the comparison between groups. Count data were indicated with the rate (%) and χ^2 test was used for the comparison between groups. The test standard $\partial = 0.05/(3-1)$ was used for the two–two comparison among the three sample rate, which is of significant difference when $P < 0.025$, and the other is of significant difference when $P < 0.05$.

Results

The baseline data of patients

The relevant baseline data including patients' age, sex ratio, prevalence of diabetes, admission systolic blood pressure, admission diastolic blood pressure, hypertension lasting time, admission NIHSS score, and admission cerebral hemorrhage volume in the tree groups were not statistically significant ($P > 0.05$), while comparable between groups, as shown in Table 1.

Table 2. On the third day of onset, serum IL-1β, IL-6, and TNF-α levels were compared.

Group	Case	IL-1β (ng/L)	IL-6 (μg/L)	TNF-α (mg/L)
Group A	40	3.52 ± 1.45**	64.51 ± 17.32*	4.95 ± 1.78*
Group B	40	3.45 ± 1.32**	65.73 ± 18.45*	5.03 ± 2.13*
Group C	80	4.68 ± 1.47	80.95 ± 1s9.36	6.04 ± 1.67
F		16.06	15.18	16.49
P		<0.05	<0.05	<0.05

IL: interleukin; TNF: tumor necrosis factor.
Compared with group D, *$P<0.05$, **$P<0.01$.

Table 3. The comparison of SP and SF levels in each group on the third day of onset.

Group	Case	SP (pg/mL)	SF (ng/mL)
Group A	40	25.41 ± 2.68**	305.96 ± 36.87*
Group B	40	25.27 ± 2.45**	307.41 ± 35.85*
Group C	80	20.64 ± 2.17	368.35 ± 31.62
F		13.62	17.04
P		<0.05	<0.05

SF: serum ferritin; SP: serum substance P.
Compared to group D, *$P<0.05$ and **$P<0.01$.

Levels of serum inflammatory cytokines in each group

On the third day of the onset, the levels of serum IL-1β, IL-6, and TNF-α in groups A and B were significantly lower than those in group C ($P<0.05$). The levels of serum IL-1β, IL-6, and TNF-α were of no significant difference between group A and group B ($P<0.05$). See Table 2.

The influence of SF and SP in each group

On the third day after onset, the level of serum SP in group A and group B was higher than that in group C ($P<0.05$), while the level of SF in group A and B was lower than that in group C ($P<0.05$), and no significant difference between group A and group B ($P<0.05$) was noted (see Table 3).

The comparison of edema volume of the patients

On the third day of onset, the volume of brain edema of patients in group A, group B, and group C was, respectively (30.45 ± 13.78) mL, (29.65 ± 14.06) mL, and (39.23 ± 15.25) mL. The volume of brain edema in group A and group B was significantly lower than in group C ($P<0.05$). There was no significant difference between group A and group B ($P>0.05$).

The changes in blood pressure in each group

On the third day after onset, the level of systolic pressure and the diastolic blood pressure in group A and group B was lower than that in group C ($P<0.05$). There was no significant difference in the indexes between the two groups ($P>0.05$). On the 30th day after onset, there was no significant difference in systolic pressure and diastolic pressure among the groups ($P>0.05$; see Table 4).

The comparison of NIHSS score and mortality in 30 days after onset

The mortality in group A, group B, and group C was, respectively, 8 cases (20.0%), 7 cases (17.5%), and 18 cases (22.5% ($P>0.05$), which is of no significant difference. The mortality in group D and group E was, respectively, 9 cases (22.5%) and 9 cases (22.5%), which was of no significant difference ($P>0.05$).

The NIHSS scores of group A, group B, and group C were 10.53 ± 3.19, 11.06 ± 3.67, and 15.14 ± 5.08 points, respectively. The scores in group A and group B were lower than those in group C. There was no significant difference between group A and group B ($P>0.05$). NIHSS scores in group D and group E were 15.05 ± 4.76 and 16.02 ± 5.21, respectively, with no significant difference between the two groups ($P>0.05$).

Discussion

At present, the treatment of hypertensive ICH is mainly aimed at reducing intracranial pressure, eliminating edema and preventing cerebral hernia. Thus, clearing the intracranial hematoma is quite important. Intracranial hematoma after hypertensive cerebral hemorrhage and the edema surrounding the hematoma is associated with inflammatory reaction, cerebral hypoxia, and brain pressure. Then, detrimental immunity is induced, and a strong immune response occurred, including the activation of B cells, T cells, and monocytes–phagocytes, and the secretion of a large number of cytokines due to irritation is also occurred.[6] TNF-α is a kind of peptide biological factors mainly produced by monocytes-macrophages, which plays

Table 4. Changes in the blood pressure of the patients in all groups (mmHg).

Group	Case	The third day		The 30th day	
		Systolic pressure	Diastolic pressure	Systolic pressure	Diastolic pressure
Group A	40	144.67 ± 19.35*	85.27 ± 15.72*	140.46 ± 18.15	82.62 ± 14.06
Group B	40	142.65 ± 18.46*	85.41 ± 15.56*	138.86 ± 19.36	83.35 ± 15.14
Group C	80	159.67 ± 16.74	96.28 ± 14.16	144.15 ± 17.22	84.91 ± 16.31
F		18.42	17.63	1.41	1.03
P		<0.05	<0.05	>0.05	>0.05
Group D	40	159.66 ± 19.32	96.04 ± 15.33	147.58 ± 14.26	85.11 ± 18.35
Group E	40	158.15 ± 17.47	95.18 ± 15.93	146.32 ± 15.37	84.95 ± 16.12
T		0.83	0.76	0.52	0.47
P		>0.05	>0.05	>0.05	>0.05

Compared to Group C, *$P < 0.05$.

significant roles in body inflammation and immune response.[7] IL-6 is a kind of inflammatory factor which can repair the nervous system and mediate immunity. The surging elevation of IL-6 can activate macrophages, damage the nervous system, damage the blood–brain barrier, and aggravate cerebral edema.[8] IL-1β can activate vascular endothelial cells and leukocytes, inducing the upregulation of intercellular adhesion molecule 1 (ICAM-1), which can enhance intercellular adhesion and enhance the inflammatory response.[9] In addition, IL-1β and IL-6 can increase NO production by increasing brain-free radical production, further changing the permeability of blood–brain barrier and aggravating the occurrence of cerebral edema.

ACEI/ARB-type antihypertensive drugs can reduce levels of a variety of inflammatory serum cytokines.[10] ACEI/ARB can inhibit the angiotensin-II-mediated expression of peroxisome proliferator–activated receptor γ (PPARγ) by inhibiting angiotensin II expression. And PPARγ is involved in the gene regulation of a variety of inflammatory factors, eventually affecting the level of serum inflammatory cytokines in patients. CCB has the role of regulating the level of inflammatory cytokines, whose possible mechanism is that CCB antihypertensive drugs can inhibit NADPH oxidase–related regulatory subunit phosphorylation to inhibit its activation and the production of reactive oxygen species (ROS), thereby reducing inflammation sexual response.

In addition, as a marker of glial injury, expression level of SF is increased caused by hypertensive ICH (HICH) inducing increased nerve damage.[11] SP level is inversely proportional to the HICH severity. The cerebral edema and cerebral anoxia after hypertensive cerebral hemorrhage reduce the SP level significantly, which in turn leads to other neurotransmitter metabolism disorders.[12] Therefore, as the SP level decreased, there is increased cerebral edema and intracranial pressure. In this study, on the third day after onset, SP level in group A and group B was significantly higher than those in group C, and SF level was lower in group A and group B than in group C. This shows that ACEI/ARB and CCB antihypertensive drugs do better to the recovery of damaged glial cells, the relief of the cerebral edema, and the reduction of intracranial pressure.

In summary, the active and regular use of ACEI/ARB and CCB antihypertensive drugs of hypertensive patients not only can reduce the damage to cardiovascular and cerebrovascular diseases and renal and other target organs but also improve the prognosis of patients with cerebral hemorrhage episodes by regulating serum inflammatory cytokines and SF, serum SP, or other ways.

Declaration of conflicting interests

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